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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,095	04/13/2004	Eiichi Ueda	KON-1870	6153

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,095	UEDA ET AL.	
	Examiner	Art Unit	
	Melissa Perreira	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/30/07 has been entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what constitutes "substantially no organic solvent" as the specification does not provide any guidance as how to determine a "substantially" acceptable amount of organic solvent.

4. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what constitutes "comprised substantially of unilamellar vesicles" as the specification does not provide any guidance as how to determine a "substantially" acceptable amount of unilamellar vesicles.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Na et al. (US 5,326,552).

7. Na et al. (US 5,326,552) teaches of phospholipids (column 2, lines 51-52; claim 5) X-ray contrast medium comprising nanoparticles containing a 2,4,6-triiodobenzoate where the surface of the nanoparticle is modified by adsorbing a nonionic polyethylene glycol, polyethylene oxide surfactants or block copolymers of propylene oxide and ethylene oxide (claim 4) which are present in the amount of about 0.1-90%, 10-30%, etc. (column 2, lines 42-53; column 4, lines 6-10; column 6, lines 34-37). The nanoparticles have an effective average size of less than 400nm or less than about 250mn (column 3, lines 47+) The method for preparing the X-ray contrast agent containing liposomes is by introducing a diagnostic agent with water and a surface modifier into a grinding vessel followed by subsequent separation (filtration) of the resulting particles and sterilization in the presence of a phospholipid. Water serves as the liquid medium and as the carrier for the agent, therefore there is no organic solvent used in the preparation of the liposomes (column 4, lines 43-47).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-18 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mackaness et al. (US 4,192,859) in view of Otake et al. (US2004/0099976A1) or Castor (US 5,554,382) and in further view of Na et al. (US 5,326,552).

10. Mackaness et al. (US 4,192,859) discloses a liposomal X-ray contrast medium having cavities containing the contrast agent therein (column 2, lines 48-52). The contrast agents suitable for use are sodium diatrizoate, iodipamide, iodamide, etc. and are present in 30-50%. The materials constituting the liposome include phospholipids (phosphotidyl choline), sterols (cholesterol) and stearylamine. The contrast medium is prepared by addition of the liposome to a buffer solution containing iodine containing contrast agent where the contrast agent is trapped within the liposome vesicle (column 3; claims 1-11 and 22). Mackaness et al. (US 4,192,859) does not disclose the use of supercritical carbon dioxide containing substantially no organic solvent or that the liposomes are unilamellar.

11. Otake et al. (US2004/0099976A1) discloses the use of supercritical carbon dioxide for the single-step preparation of unilamellar liposomes, 50nm to 80nm in diameter that encapsulate a desired substance without the use of harmful organic

solvents (abstract; p3, [0035]). The liposome preparation involves adding an aqueous solution (to be encapsulated) to a mixture of a phospholipids and/or glycolipid and carbon dioxide under super critical conditions (p1, [0019]-[0020]; p2, [0021] and [0028]-[0029]). This preparation does not require the addition of a cosolvent but optionally can include a cosolvent (p3, [0035]) and the liposomes of the present invention are free of harmful organic solvents and toxicity caused by such solvents (p3, [0037]). Carbon dioxide under super critical condition is meant to represent carbon dioxide at or above critical temperature (30.98°C) and pressure (7.3773 Mpa) (p2, [0022]).

12. Castor (US 5,554,382) discloses the method of producing unilamellar (column 4, line 34) liposomes that are substantially free of organic solvents in supercritical CO_2 (column 2, lines 50-56; column 3, line 35). The method of preparing the liposomes involves mixing phospholipids in an aqueous phase (optionally containing a therapeutic agent) with a supercritical CO_2 (column 3, lines 41-47; column 9, lines 28-31). The resulting liposomes can be filtered through a 0.22 micron filter to reduce the 0.06mm critical fluid liposomes by 50% to yield liposomes of size 105 nm (column 10, lines 60-61).

13. Na et al. (US 5,326,552) teaches of X-ray contrast medium comprising nanoparticles containing a 2,4,6-triiodobenzoate where the surface of the nanoparticle is modified by adsorbing a nonionic polyethylene glycol, polyethylene oxide surfactants or block copolymers of propylene oxide and ethylene oxide (claim 4) which are present in the amount of about 0.1-90%, 10-30%, etc. as well as that listed above.

14. It is respectfully pointed out that instant claim 2,9 and 17-20 are product-by-process limitations. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

15. At the time of the invention it would have been obvious to one ordinarily skilled in the art to modify the surface of the liposomal vesicles of Mackaness et al. with the polyethylene oxide (PEO) of Na et al. to provide liposomes with targeted site-specificity and images of exceptional resolution (see Na et al., column 1, lines 53-60). The inclusion of the surface modifier, such as PEO overcomes the charge effect imparted by the phospholipid to the liposome which causes the liposome to be cleared from the blood faster (see Na et al., column 2, lines 3-34). Also the surface modifiers are used to control the interfacial tension between the phospholipids solution and water to facilitate the generation of the liposome vesicle with the desired particle size. At the time of the invention it would have been obvious to one ordinarily skilled in the art to prepare the modified liposome of the combined disclosures above via the supercritical carbon dioxide preparation method of Otake et al. or Castor since it makes it possible to produce these modified unilamellar liposomes with improved trapping efficiency in fewer steps and without using harmful organic solvents. The extreme conditions used with

multiple step syntheses using harmful organic solvents can cause the denaturation of the phospholipids raw material. The preparation of the liposomes containing iodinated contrast medium of the combined disclosures encompasses that of the instant claims and therefore generates liposomes containing iodinated contrast agents that encompass those of the instant claims which should be capable of satisfying the same requirements.

16. Claims 1-26 rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al (US 5,676,928) in view of Otake et al. (US2004/0099976A1) or Castor (US 5,554,382) and further in view of Na et al. (US 5,326,552).

17. Klaveness et al (US 5,676,928) discloses a liposomal contrast agent encapsulating an iodine imaging agent (iodixanol) for use in X-ray (claims 13 and 14). These unilamellar liposomes (column 9, lines 36-50) have a high encapsulation capacity, 5-6 ml/g and a typical concentration of 10-300mg of encapsulated iodine per ml composition. The iodine imaging agent is contained within the liposome and the liposome suspended in an aqueous medium containing the same iodinated imaging agent and a buffering solution (column 4; column 8, lines 3-9). Any biocompatible gas, such as carbon dioxide or stabilizing agent, such as $EDTANa_2Ca$ or Trometamol may be present (column 6, line 1; column 10, line 23; example 8). The total lipid concentration is generally 20mg/ml to 100mg/ml (column 7, lines 64+). In an effort to obtain the desired particle size, 50nm to 3000nm the liposomes may be passed through a filter with a predetermined pore size (column 9, lines 28-33). The weight ratios and

particle size disclosed encompass those of the instant claims. Klaveness et al (US 5,676,928) does not disclose the modification of the phospholipid with a polyalkylene oxide or the preparation of the liposomes with supercritical carbon dioxide.

18. Otake et al. (US2004/0099976A1) discloses the use of supercritical carbon dioxide for the single-step preparation of unilamellar liposomes, 50nm to 80nm in diameter that encapsulate a desired substance without the use of harmful organic solvents (abstract; p3, [0035]). The liposome preparation involves adding an aqueous solution (to be encapsulated) to a mixture of a phospholipids and/or glycolipid and carbon dioxide under super critical conditions (p1, [0019]-[0020]; p2, [0021] and [0028]-[0029]). This preparation does not require the addition of a cosolvent but optionally can include a cosolvent (p3, [0035]) and the liposomes of the present invention are free of harmful organic solvents and toxicity caused by such solvents (p3, [0037]). Carbon dioxide under super critical condition is meant to represent carbon dioxide at or above critical temperature (30.98°C) and pressure (7.3773 Mpa) (p2, [0022]).

19. Castor (US 5,554,382) discloses the method of producing unilamellar (column 4, line 34) liposomes that are substantially free of organic solvents in supercritical CO_2 as well as that listed above.

20. Na et al. (US 5,326,552) teaches of X-ray contrast medium comprising nanoparticles containing a 2,4,6-triiodobenzoate where the surface of the nanoparticle is modified by adsorbing a nonionic polyethylene glycol, polyethylene oxide surfactants or block copolymers of propylene oxide and ethylene oxide (claim 4) which are present in the amount of about 0.1-90%, 10-30%, etc. as well as that listed above.

21. It is respectfully pointed out that instant claims 2,9 and 17-20 are product-by-process limitations. Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed Cir. 1985). See MPEP 2113.

22. At the time of the invention it would have been obvious to one ordinarily skilled in the art to modify the phospholipids of Klaveness et al (US 5,676,928) with polyalkylene oxides as disclosed by Na et al. (US 5,326,552) to control the interfacial tension between the phospholipids solution and water to facilitate the generation of the liposome vesicle with the desired particle size and it would be obvious to use a commercially available filter with the correct size pores to isolate these desired particles.

23. At the time of the invention it would have been obvious to one ordinarily skilled in the art to prepare this modified liposome via the supercritical carbon dioxide preparation method of Otake et al. (US2004/0099976A1) or Castor since it makes it possible to produce these modified unilamellar liposomes with improved trapping efficiency in fewer steps and without using harmful organic solvents. The extreme conditions used with multiple step syntheses using harmful organic solvents can cause the denaturation of the phospholipids raw material. The preparation of the liposomes containing iodinated contrast medium of the combined disclosures encompasses that of the instant claims

and therefore generates liposomes containing iodinated contrast agents that encompass those of the instant claims which should be capable of satisfying the same requirements.

Double Patenting

24. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

25. Claims 21,22 and 25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4,6 and 8-10 of copending Application No. 11/180849. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of preparing a radiographic contrast medium comprising unilamellar liposomes of the instant claims encompasses the method of preparing a radiographic contrast medium of the

copending application 11/180,849 whereas both contain the steps of mixing a polyalkylene oxide modified phospholipid and a sterol with an aqueous solution containing a water-soluble iodine compound via supercritical carbon dioxide. The specie of iopamidol, iohexol, etc. of 11/180,849 anticipates the genus of non-ionic iodine compound of the instant claims and the method of preparation of 11/180,849 does not describe the use of organic solvent but does describe the use of aqueous solutions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Claims 21,22 and 25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,5-7,11,12 and 14-17 of copending Application No. 11/187,397. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of preparing a liposome containing a water-soluble iodine compound, sterols and polyalkylene compounds via supercritical carbon dioxide under increased temperature and pressure of the instant claims is also disclosed in the claims of the copending application 11/187,397. The method of preparation of 11/187,397 does not describe the use of organic solvent but does describe the use of aqueous solutions which encompasses the method of the instant claims. Filtration of the desired iodine containing liposomes is also disclosed in both applications as is the method for preparing such liposomes listed above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melissa Perreira whose telephone number is 571-272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MP
May 1, 2007

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER